REMARKS/ARGUMENTS

Claims 1, 3-5 and 8-15 remain in the present application and have been amended. New claims 16 to 30 have been added to the application. In support of the remarks and arguments set forth herein, the Applicant submits herewith as an attachment to this Amendment, a Declaration of Thomas Rausch, with exhibits, under 37 C.F.R. §1.132, dated November 24, 2007 ("Rausch Decl."). Also enclosed is a copy of the reference, Krausgrill et al. 1998 Plant J 13: 275-280, which is referred to at page 6, line 14 of the Rausch Decl. The claim amendments and new claims presented herein are all entirely supported by the application as originally filed and, thus, they raise no issue of new matter.

In addition, Applicant submits together with this Amendment and response a Request for Continued Examination and, pursuant to the same, requests that this Amendment and response be entered into the record.

At pages 2-3 of the present Office Action, the Examiner has rejected claims 1, 3-5 and 8-15 as not being supported by a sufficient written description under 35 U.S.C. § 112, first paragraph. The Examiner's position is that the Applicant has not demonstrated that he is in possession of the invention as broadly claimed. Specifically, page 2 of the Action asserts that the claims contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention" for the reasons set forth "in the office action filed 10/02/2006." In the 10/02/2006 Office Action, it was asserted, *inter alia*, that Applicant's specification did not sufficiently describe "structural features common to members of the claimed genus of sequences expressed during seed development in flowers with young ovules," as required by the second of two tests set forth in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

In response to the 10/02/2006 Action, the Applicant filed a response dated April 2, 2007 which amended the claims to call for an "apoplastic" invertase inhibitor protein. The response pointed out that that one of ordinary skill in the art, upon reading the specification, would find common structural features to members of a genus of sequences expressed during seed

development in flowers with young ovules. Applicant further pointed out that that proteins falling within certain classes show a high degree of homology. See April 2, 2007 Response at page 9. Nevertheless, the Examiner in the present Action continues to maintain the rejection of the claims, stating that "[a]pplicant's remarks are about structural features common to sequence expressed during seed development and not apoplastic invertase inhibitors." As shown above in the listing of the Claims, in the present Amendment Applicant has further amended the claims to call for "endogenous" apoplastic invertase inhibitor protein.

Applicant respectfully traverses these rejections in light of the present amendments to the Claims. It is Applicant's position that there are indeed structural features common to the members of the genus of endogenous apoplastic invertase inhibitors.

Applicant's position is supported by the evidence contained in the Rausch Decl. submitted together with this Response.

In preparation for giving the opinions and data in his declaration, Dr. Rausch has searched and consulted the literature relevant to the topic of his declaration, and the research and data generated in his own research group over the period 1999-2007.

While the molecular biology of invertase inhibitors is a research field largely dominated by the studies carried out by Dr. Rausch's group, several additional papers by third parties have independently confirmed the importance of a tight invertase regulation during the process of seed filling for different plant families, as demonstrated by Dr Rausch's and his colleagues' work in oil seed rape, the work in maize done by Bate and others (Rausch Decl. Exhibit 2), the work by Weschke and others in barley (Rausch Decl. Exhibit 3) and the work by Weber and Wobus in *Vicia faba* (Rausch Decl. Exhibit 4).

To assist the Examiner with scientific support for Applicant's claims, Dr. Rausch has conducted a multiple sequence alignment analysis of several plant invertase inhibitor sequences. This analysis demonstrates that "plant invertase inhibitors form a clearly defined genus of proteins." (Rausch Decl., page 5, ¶ 16). Further, Dr. Rausch has found and confirmed that "[o]nce a putative invertase inhibitor from a given plant species has been cloned, it is possible to identify it as a member of the 'invertase inhibitor genus' by sequence comparison with other functionally confirmed invertase inhibitors . . . " Id.

As Dr. Rausch explains, "[p]lant invertase inhibitors are a small, distinct and well-defined subgroup of the larger protein family of pectin methylesterase inhibitor-like genes . . . ." (Rausch Decl., page 4, ¶ 15). Moreover, research in the art has established that the invertase inhibitor sub-group is clearly separated from pectin methylesterase inhibitors. (Rausch Decl., page 5, ¶ 16).

In comparing and analyzing tobacco cell wall and vacuolar inhibitors against and with a number of other plant invertase inhibitor protein sequences from different plant families, Dr. Rausch has found that they are, "characterized by 4 cysteine residues in highly conserved positions." See Rausch Decl., pages 4-5, ¶ 15 and sequence alignments illustrated at page 5 (highlighted portions). Further, an examination of Dr. Rausch's sequence alignment data (see highlighted portions) reveals that a number of species have common structural features in addition to cysteine, e.g., TCK (first cluster), Y (second cluster) and F (third cluster). (Rausch Decl., page 5, ¶ 15).

Based upon these data, and Dr. Rausch's research and experience, "[a]ll functionally confirmed invertase inhibitors (at least within dicot plants) cloned over the last few years (chicory, sugar beet, *Arabidopsis,* oil seed rape, tobacco, soybean etc.) [are grouped] with the invertase inhibitor sub-group of *Arabidopsis thaliana*, and are therefore clearly separated from pectin methylesterase inhibitors." In sum, "plant invertase inhibitors form a clearly defined genus of proteins." (Rausch Decl., page 5, ¶ 16).

Most importantly, however, Dr. Rausch has confirmed that, "[o]nce a putative invertase inhibitor from a given plant species has been cloned, it is possible to identify it as a member of the 'invertase inhibitor genus' by sequence comparison with other functionally confirmed invertase inhibitors, and via its position in the evolutionary tree of pectin methylesterase inhibitors from *Arabidopsis thaliana*." (Rausch Decl., page 5, ¶ 16).

The points made above by Dr. Rausch comport with the Federal Circuit's decision in *Enzo Biochem, Inc. v. Genprobe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002)("*Enzo II*"). *Enzo II* established that the rule set forth in *University of California*, cited by the Examiner in the Action, is <u>not</u> universal. In particular, the Federal Circuit in *Enzo II* held that a disclosed sequence species structure, and/or related claimed or disclosed functional language,

may support a claim to a corresponding genus if the species is representative of the genus, or if the claimed function can be tied to a known or disclosed structure. *Enzo II*, 296 F.3d at 1324-1328. Dr. Rausch demonstrates that both standards are met in the present application.

As set forth above, Dr. Rausch demonstrates that the disclosed tobacco invertase inhibitor sequences are representative of the claimed genus. In addition, Dr. Rausch also demonstrates below that the ties between the structural and functional aspects of invertase inhibitor proteins have been established. In particular, the analyses of structure-function relationships in the relevant genus of invertase inhibitors have confirmed the role of two intramolecular disulfide bridges and a unique N-terminal hairpin structure, which is structurally aligned with the four-helix-bundle. (Rausch Decl., page 5, ¶ 17, Exhibits 5 and 6). In particular, certain amino acids may be replaced by others, as long as important structural features, e.g., conserved cysteine residues involved in attaching the hairpin to the core structure, are not compromised. When using related/mutated nucleotide sequences to a given invertase inhibitor in a crop plant species of interest, antisense or RNAi-constructs of such related/mutated sequences will be effective as long as perfectly conserved stretches of 21-25 nucleotides are included. This is common knowledge. Therefore, the claim for down-regulation of a particular invertase inhibitor via antisense or RNAi always has to include derived nucleotide sequences known to perform the same function as the original, endogenous sequence. (Rausch Decl., pages 5-6 ¶ 17).

Therefore, based upon the representative plant inhibitor invertase species analysed by Dr. Rausch, the endogenous apoplastic inhibitor invertase from tobacco exhibits known structural and functional features common to the members of the genus of sequences falling within the claims which are the subject of this application. Applicant therefore respectfully submits that, on the bases set forth in the Rausch Declaration, that the rejection of claims 1, 3-5 and 8-15 based upon an alleged insufficient written description be withdrawn.

There are, moreover, several additional reasons why the subject rejection should be withdrawn.

In the Action, the Examiner noted the inclusion in claims 1, 3-5 and 8-15 of an "apoplastic" invertase inhibitor, but he apparently has objected to the claim language stating that the nucleotide sequence is a nucleotide sequence having a 80% sequence identity to a cDNA

from a cDNA library from flowers with young ovules of a plant. (See Action, page 2 to top of page 3). The Action further states that the inclusion of "a cDNA library" element calls for, "an invitation to go fishing for sequences rather than a demonstration of possession of the invention as broadly claimed." See Action, page 3.

The Applicant respectfully submits that claim 1, and thus the dependent claims, as now amended, overcome this aspect of the written description objection raised in the Action. In particular, presently amended claim 1 now refers to a nucleotide sequence coding for "the **endogenous** apoplastic invertase inhibitor protein," "or a nucleotide sequence having a sequence identity of 80% or more to said nucleotide sequence coding the **endogenous** apoplastic invertase inhibitor protein." As shown in the amendments, the reference to "a sequence identity to a cDNA library," etc., has been removed from the claims.

To buttress the data and opinions of Dr. Rausch, the reference to endogenous apoplastic invertase inhibitor protein clearly defines the scope of the claims for the skilled worker by its demonstration of the ties between structure and function. Moreover, however, the relevant proteins are those with endogenous apoplastic invertase inhibitor activity, which thus clearly direct the skilled worker to the source of the proteins, i.e., the nucleotide sequences expressed during seed development in flowers with young ovules. In short, clarification of the description of the claims is made by the fact that the plant cells to be transformed are plant cells of a plant from which the coding nucleotide sequence was obtained. Thus, the invention is thereby defined for the full scope of the Claims. Together with the representative nucleotide sequences set forth in the specification, it is respectfully submitted that Claims 1, 3-5 and 8-15, as now amended, are supported by the disclosures contained in the specification.

Another important point is respectfully submitted to the Examiner. The instant application is a continuation-in-part of U.S. Patent Application No. 09/762,782, which was filed on March 30, 2001 and which issued as U.S. Patent No. 6,784,339 to Thomas Rausch ("Rausch Application" and "Rausch Patent", respectively). The Rausch Patent is directed to transgenic plants and plant cells comprising a reduced expression of invertase inhibitors. The claims of the Rausch Patent bear similarity to the instant claims, one exception being that in the prior application the coding sequence is inserted in a DNA construct in an anti-sense orientation, as

opposed to a sense orientation as set forth in the instant claims. See, e.g., Rausch Patent Col. 10, line 63 to Col. 11, line 18. Dr. Thomas Rausch is the same inventor of the invention described and claimed in the instant application, and the present Examiner examined the Rausch Application and allowed the claims therein.

Importantly, the Examiner is respectfully referred to the specification of the Rausch Application, the claims of which were ultimately granted without the requirement that the specification disclose multiple nucleotide sequences expressed during seed development of different plants. Nor was there any requirement to limit the claims of the Rausch Application to a specific plant species. Thus, it is respectfully submitted that the same reasoning should be applied to the pending claims of the instant application, and that its claims, as now amended, should be granted.

For all of the above reasons, it is, again, respectfully submitted that the rejection of claims 1, 3-5 and 8-15 of the instant application on written description grounds be withdrawn.

The Examiner has also rejected claims 1, 3-5 and 8-15 as not fully enabled under 35 U.S.C. §112, first paragraph. Here, the Examiner has stated that the claims are enabled, "for a process for producing a transgenic plant where the seed have an increased amount of reserves by transforming with the isolated endogenous apoplastic invertase inhibitor coding sequence in sense orientation, bearing seed with increased reserve content . . .." See Action, page 3. However, the Action further states that the claims do not, "reasonably provide enablement for a process of inhibiting invertase in a plant by transforming the plant with a sequence having 80% sequence identity to an apoplastic invertase coding sequence expressed during seed development in flowers with young ovules" for the full breadth of the claims. *Id.* Further, the Examiner disagreed with the Applicant's proposition that the art of isolating DNA sequences is mature and that one of ordinary skill in the art could derive similar materials and methods for producing other transgenic plants without undue experimentation, citing *Genentech, Inc. v. Novo Nordisk, A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997). Action page 4. Thus, the Examiner appears to have taken the view that the claims are partially enabled, but not fully.

Dr. Rausch's research and scientific opinions, however, demonstrate, as set forth in his declaration, and as summarized below, that the isolation and purification of the inhibitor protein,

primer design, derivation and cloning of the corresponding cDNA and transformation of a plant species with a suitable construct containing all or part of the cDNA is routine. See Rausch Decl, 6-8, ¶¶ 19-22.

In his Declaration, Dr. Rausch sets forth in great detail streamlined experimental methods used to achieve transformation of any relevant plant species (Rausch Decl., pages 6-7, ¶¶ 19-21) and concludes that the approach for the isolation of a particular invertase inhibitor protein impacting on the seed filling process in a given plant species is straight forward and exclusively uses standard methods in molecular biology. (Rausch Declaration, page 6, ¶ 19). In sum, "the entire streamlined procedure does indeed not involve any non-standard protocol. The initial purification of inhibitor protein can be performed in 2-4 days in any protein biochemistry lab equipped for standard operations. Having obtained the results from mass-spectrometric analysis, the subsequent cloning of a full-length inhibitor cDNA can be accomplished in 2-3 days. Again, standard PCR reactions and RACE protocols do not require excessive experimentation. In my laboratory, this approach has been successfully implemented for tobacco and for sugar beet." (Rausch Decl., page 7, ¶ 20).

Further, with respect to most of the plant species illustrated in claim 12, Dr. Rausch found that, "transformation protocols based on gene delivery via *Agrobacterium tumefaciens* exist and are published. Therefore, stable plant transformation with a construct including any part of invertase inhibitor cDNA sequence in sense or antisense orientation (or as RNAi construct) and an appropriate promoter sequence *can be regarded as established technology* (with some specific variations depending on the species of interest; the respective procedures can be executed by any trained technician). Meanwhile, the approach described for tobacco has been extended to oil seed rape and basically given similar results as concluded from a first preliminary analysis of transformants. (Rausch Decl., page 7, ¶ 21, and Exhibit 7, Declaration of Thomas Rausch under C.F.R.§1.132 submitted in the prosecution of the Rausch Application. (Emphasis added).

Importantly, Dr. Rausch points out that the isolation of a novel invertase inhibitor from a given plant species follows exactly the procedures described for tobacco, since the characteristics of invertase inhibitors, on which the isolation and cloning procedures are based, extend to the

entire genus of plant invertase inhibitors. (Rausch Decl., page 7, ¶ 22). This point has a sound foundation in Dr. Rausch's exhaustive treatment of the present state of the knowledge in the art regarding invertase activity among different plant species and families. (Rausch Decl., pages 7-8, ¶ 22).

Thus, it is respectfully submitted on these bases that the enablement requirement has been satisfied.

In addition, however, as noted above, the claims have been amended. Independent claim 1, the sole original independent claim, now refers to a nucleotide sequence coding for, "the endogenous apoplastic invertase inhibitor protein", "or a nucleotide sequence having a sequence identity of 80% or more to said nucleotide sequence coding the endogenous apoplastic invertase inhibitor protein."

With respect to the express teachings of the specification, it is respectfully submitted that the fact that the present claim 1 now also includes a nucleotide sequence having an 80% identity to a specific nucleotide sequence coding for the endogenous apoplastic invertase inhibitor protein, the enablement requirement is satisfied. The specification teaches mutated sequences of the endogenous apoplastic invertase inhibitor, which shows that deviations or mutations in the nucleotide sequence still lead to the desired result of increasing seed reserves. See specification, page 26, Table 5 and Figure 8 (base substitutions indicated). Thus, amended claim 1 also provides clarification as to which specific sequence the 80% or more sequence identity is calculated.

Thus, the present application enables the generically claimed plant species due to the fact that, for rape and tobacco, examples are disclosed to provide support for the enablement of the 80% or more sequence identity recitation in claim 1, especially given the teachings, *inter alia*, in the experiments reflected in Table 5 relating to mutations of the specifically disclosed nucleotide sequence.

To further underscore the enablement of the claims, the Examiner is also respectfully referred to page 23, lines 8-12, of the specification wherein, in addition to tobacco, there is, as a further example, the introduction of an invertase inhibitor construct in rape. The result of the invertase inhibitor transformation in rape is an increase in the stored oil content by at least 20%

and possible by up to 70%.

Further, page 24 of the specification discloses that further experiments show that nucleotide sequences which are not completely identical to the endogenous invertase inhibitor protein gene can be used to increase the amount of reserve material in transgenic plants (see, for example, page 24, lines 17 to 20 of the specification). Therefore, the specification teaches that additional nucleotide sequences show a high degree of homology to the nucleotide sequence of the endogenous invertase inhibitor and thus enable the claimed method of the present invention.

In addition, with respect to the enablement of the "80% or more sequence identity" recitation in the claim, the specification demonstrates that an homology of at least 20 to 25 base pairs is sufficient as a homologous region in order to eliminate or reduce the expression of the endogenous invertase inhibitor gene (see page 24, lines 20 to 27 of the specification). Further, mutated or homologous nucleotide sequences which do not encode a functional invertase inhibitor protein can be used in transgenic plants in order to eliminate or reduce the expression of the endogenous invertase inhibitor protein during the development of seeds, and consequently, to increase the amount of reserve material in seeds (see specification at page 25, lines 7 to 14).

In sum, Applicant submits that the disclosures of the specification clearly do provide a sufficient basis for the enablement of the process of presently amended Claim 1.

Finally, further with regard to the issue of enablement, the Action cites *Genentech, Inc. v. Novo Nordisk, A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997) in support of the objection to Applicant's point that the art is mature with respect to isolating DNA sequences and deriving similar materials for producing other transgenic plants without undue experimentation. See Action page 4. Applicant respectfully traverses this point for the following reasons. At issue in *Genentech* was whether one of ordinary skill in the art could purify a human growth hormone conjugate protein using cleavable fusion expression at the time of the filing of the subject patent application, *July 5, 1979. Genentech*, 42 USPQ2d at 1004. The Federal Circuit held that the use of enzymes to cleave conjugate-hGH was not known in the art in 1979 because "the claimed invention is the application of an unpredictable technology in the early stages of development." Id. at 1006. Were it otherwise, as the Court noted, the applicable rule is, "that a specification need not disclose what is well known in the art." Id. at 1005.

The present application was filed in 2004, 23 years after the filing of the application in *Genentech*. The biotechnology arts have greatly developed in the past 23 years, including methods for isolating, cloning and sequencing DNA and transforming cellular entities with DNA containing constructs to achieve results like those of the present invention. Thus, it is submitted that one of ordinary skill in the art, with the benefit of the teachings in the instant application, could isolate and use the nucleotide sequences in accordance with the claimed invention.

Thus, Applicant respectfully submits that the rejection of Claims 1, 3-5 and 8-15 on nonenablement grounds should be withdrawn.

The Examiner has additionally rejected the claims under 35 U.S.C. § 112, second paragraph, based on the assertion that the claims are indefinite because they claim a percent identity to sequences, the identity of which are not disclosed (i.e. a sequence identifier), and thus there is no measure of the metes and bounds of 80% sequence identity.

Applicant respectfully traverses this rejection. It is well understood that claims are to be interpreted in light of the specification. The present specification is replete with disclosures and detailed descriptions of varying sequence identities and homologies. See, for example, the specification at page 5, line 25 to page 6, line 5; page 6, line 24 to page 7, line 7; page 7, line 25 to page 8, line 12; page 11, lines 13-19, and page 24, line 17 to page 25, line 14. Thus, it is submitted that one of ordinary skill in the art, reading the claims in light of the specification, would clearly and definitely understand the identities of the percent sequence identities contemplated and taught by the present application.

Thus, Applicant respectfully submits that the rejection of the Claims on indefiniteness grounds should be withdrawn.

In addition, Applicant has amended Claims 3-5 and 8-5 to recite, solely for grammatical reasons, "The" process instead of "A" process.

New Claims 16 to 30 are proposed for entry into the instant application. These claims, generally speaking, relate to the RNAi mechanism which leads to a post-transcriptional silencing of the endogenous invertase inhibitor gene. Support for claims 16 to 30 is found on page 8, line 27 to page 9, line 24 of the specification and thus they raise no issue of new matter. The nucleotide sequence according to claim 16 in step a) does not necessarily refer to a coding sequence, but refers

to any nucleotide sequence of the apoplastic invertase inhibitor protein gene, including fragments thereof. This means that the nucleotide sequence may be a full-length sequence or only a partial fragment of the apoplastic invertase inhibitor protein gene. For the RNAi approach it is not necessary to use the full-length coding sequence since fragments of 21 to 25 base pairs may also silence the target gene (see page 9 of the specification).

Summary

The Examiner is respectfully requested to enter this Amendment and Response since a Request for Continued Examination is also being filed herewith. With respect to current Claims 1, 3-5 and 8-15, the Examiner is respectfully requested to reconsider and withdraw all of the rejections set forth in the Action in light of the claim amendments and remarks presented herein. With respect to new Claims 16 to 30, the Applicant respectfully requests that the same be added to the application and submits that they are all believed to be in condition for allowance. If the Examiner does not agree, and believes that an interview would advance the progress of this application, he is respectfully invited to telephone applicant's representative at the number below so that such an interview may be scheduled.

EXPRESS MAIL CERTIFICATE
I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee (mail label #EV889348992US) in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on November 28, 2007:

Dorothy Jenkins

Name of Person Mailing Correspondence

Dorothy Jenkins

Signature

November 28, 2007

Date of Signature

MAF/JMM:jl/lac

Respectfully submitted,

Mark A. Farley

Mark A. Farley
Registration No.: 33,170
OSTROLENK, FABER, GERB & SOFFEN, LLP
1180 Avenue of the Americas
New York, New York 10036-8403
Telephone: (212) 382-0700